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Atty. Docket No. CST-213
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Bacus *et al.*
ASSIGNEE: CELL SIGNALING TECHNOLOGY, INC.
SERIAL NUMBER: 10/735,118 EXAMINER: Susan Ungar, Ph.D.
FILING DATE: December 11, 2003 ART UNIT: 1642
FOR: METHOD FOR PREDICTING RESPONSE TO HER-2 DIRECTED THERAPY

December 20, 2006
Danvers, Massachusetts

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-14500

**RESPONSE TO RESTRICTION REQUIREMENT AND REQUEST FOR
RECONSIDERATION
(37 C.F.R. §1.143; §1.111; §1.143)**

This paper is filed in response to the October 4, 2006 Restriction Requirement issued in the above-identified patent application and is a written follow-up to a telephonic interview with the Examiner held on November 30, 2006.

A Petition for a two (2) month extension of time under 37 C.F.R. §1.136(a) is being filed concurrently with this Response. The Commissioner is hereby authorized to charge the required fee (small entity) of \$225.00, pursuant to 37 C.F.R. §1.17(a)(2), along with any other fees that may be due, to Deposit Account No. 50-1774, Ref. No. CST-213. With the extension, the present paper is due on or before January 4, 2007.

REMARKS

In the outstanding Office Action the Examiner has required restriction between the subject matter of group A (claims 84-88, 89-92, 99-101, 103, and 105-107), group B (claim 89 and 93-107), and group C (claims 108-110). Within each group the Examiner has further required restriction between the recited Markush group of species. The Examiner alleges that the claimed subject matter of each group is both independent and distinct, and that restriction is

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therefore proper. Applicants respectfully disagree and submit that the required restriction unduly limits Applicants' invention to only certain preferred embodiments and species, and is thus improper. Applicants respectfully request that the Examiner reconsider the outstanding restriction for the reasons outlined in a Telephonic interview conducted with the Examiner on November 30, 2006, which is summarized below.

Summary Of The Interview

Pursuant to 37 C.F.R. §1.133(b), Applicants provide the following summary of the telephonic interview between the Examiner and the undersigned attorneys held on November 30, 2006. During the interview, Applicants' attorney indicated his concern with the outstanding restriction requirement, since the subject matter as claimed is in fact simply preferred embodiments of a single unitary invention: The identification of six proteins whose expression/activity has been identified by Applicants as being correlated to the responsiveness of HER-2 over-expressing tumors to HER-2 therapeutics, and the use of such proteins as predictive biomarkers.

At the start of the interview, Applicants' attorney first informed the Examiner that Applicants will voluntarily elect not to pursue (without traverse) the subject matter of group A (with respect to claims 84-88) and group C (claims 108-110), notwithstanding Applicants' position that the restriction between these groups and group B is improper and unsustainable. Applicants' attorney informed the Examiner that the subject matter of claims 90-92 (which depend from and further limit independent claim 89) should properly be considered together with independent claim 89 as part of group B (along with dependent claims 93-107).

Respecting the subject matter of group B (claim 89 and 93-107, as well as claims 90-92) Applicant's attorney first stressed to Examiner that the six individual protein biomarkers recited in parts (a)-(f) of claim 89 (as well as dependent claims 90-107) are not independent or distinct inventions as defined by § 802.01 of the M.P.E.P. Rather, these six biomarker proteins are part of a *single* patentable invention (a method of identifying tumor responsiveness by detecting the presence of such biomarkers) and should not be subject to restriction (beyond a requirement for a provisional election of species for the recited Markush group). Section 802.01 of the M.P.E.P. defines independent inventions as having "*No disclosed relationship.*" Applicants' attorney

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pointed out to the Examiner that the six biomarkers recited in claim 89 in fact have the disclosed relationship of being predictive of whether a patient or tumor will respond to a HER-2 directed therapy. Indeed, the discovery leading to the invention (as described in the specification) was that these particular six proteins, out of a great many more proteins involved in signaling pathways within HER-2 over-expressing tumors, are in fact correlated to drug responsiveness and therefore useful as biomarkers. Similarly, distinct inventions are defined, in M.P.E.P. §802.01, as inventions that "*as claimed, are not connected in at least one of design, operation or effect* and wherein at least one invention is patentable over the other." Applicants' attorney explained to the Examiner that the 6 biomarkers recited in claim 89 are in fact disclosed in the specification as being connected in *both operation and effect*. The method of the present invention is a collection of six biomarkers which, when analyzed together, are predictive of response/non-response to HER-2 directed therapy in a specific type of tumor. The six markers, whether taken individually or collectively, *operate* to predict response or non-response. Additionally, by detecting overexpression and/or activation of the markers, whether individually or collectively, the same physiological *effect* (*i.e.* response or non-response to a HER-2 directed therapy) is achieved.

In short, the six biomarker proteins recited in subparts (a)-(f) of claim 89 share common features and characteristics, and are connected in operation and effect. Accordingly, there is but one invention (not multiple independent and distinct inventions) claimed in claim 89 (and its dependent claims 90-107), and Applicants' respectfully request the outstanding restriction of this subject matter be reconsidered and withdrawn.

Applicants' attorney further asserted to Examiner that the six species (biomarkers) recited in claim 89 are properly linked so as to constitute proper Markush format and thus Applicants are entitled to retain this reasonable number of species in their claim. See MPEP §806.04, 37 CFR 1.141. Applicants' attorney respectfully suggested that Examiner has misapplied § 803.02 of the MPEP in the outstanding Restriction Requirement by asserting, "*compounds [recited as 'entities' by examiner] included within a Markush group must share substantial structural feature disclosed as being essential to utility of the Markush group.*" (See October 4, 2006 Restriction Requirement at p. 3, first paragraph). Indeed, the preceding italicized sentence of

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§803.02 speaks to claims for chemical compounds, *not* biotechnology method claims as in the present case.

The portion of § 803.02 that speaks to the present technology states that “* * * *when the Markush group occurs in a claim reciting a process or combination (not a single compound), it is sufficient if the members of the group are disclosed in the specification to (1) possess at least one property in common which is mainly responsible for their function in the claimed relationship and (2) it is clear from their very nature or from the prior art that all of them possess this property.*” Here, the invention as claimed satisfies this test. Applicants’ attorney pointed out that the present specification discloses that all six of the proteins in the group as having the common property of being indicative or response/non-response to a HER-2 directed therapy. Applicant’s attorney also pointed out that it is quite clear from the experiments disclosed in the present specification that all six markers do, in fact, possess this property of being predictive of response/non-response. These six proteins are in fact, by their very nature, biomarkers of HER-2 inhibitor responsiveness as claimed, but it remained for Applicants’ to identify that their altered expression or activation was correlated to such responsiveness, out of a great many other candidate proteins which Applicants have shown are not biomarkers.

Applicants’ attorney therefore argued that Applicants’ should be allowed to retain the six biomarker proteins as species of a Markush group as defined in claim 89 as presently written, and to merely make a provisional election of a preferred species in the event that the Examiner finds the generic claim not allowable. Accordingly, the Examiner was informed that Applicants would make such provision species election (of IFGR together with NDF) upon filing of this Response.

Applicant’s Attorney also reminded the Examiner that a restriction requirement should only be maintained in those instances where there would be a “serious burden” if restriction was not required. See M.P.E.P. §803. Here, searching and examining the species within the Markush group of biomarkers recited in claim 89 would *not* impose an undue burden on the Examiner. Firstly, the Examiner herself has noted these species are all in the same class (Class 435) of search. Secondly, the Examiner was informed she can readily search the subject matter without undue burden simply using a search string that incorporates key elements of the claimed invention (“HER-2”, “therapy”, “response” and one or more of the recited biomarkers), which

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search would readily pull up prior art disclosing at least one of the recited proteins as a biomarker. The Examiner can then determine whether such reference teaches or suggests all elements of the claim. Indeed, Applicants have already conducted their own prior art searches with great success and little burden employing just such a search strategy.

Finally, Applicant's attorney brought to Examiner's attention the existence of another application (owned by Applicant) presently pending in the same Art Unit (1600) of the USPTO with claims substantially similar in structure to the present claims (that case also claims a method for predicting response by detecting one or more of a limited number of biomarkers recited in Markush format). Applicants' attorney highlighted the fact these other claims have properly *not* been subject to restriction and, therefore, claims 89-107 of the present application should similarly not be subjected to restriction either (beyond a requirement for provisional election of species). Moreover, claims 89-107 should not be subject to restriction for the sake of consistency between substantially similar cases presently pending before the USPTO; Applicants are entitled to expect similar treatment for similar claims within the 1600 Art Unit.

Near the end of the interview Applicants attorney and Examiner discussed the possibility of Examiner changing her restriction, as it presently relates to claim 89 and its dependent claims, from a requirement of restriction between groups to simply requiring a provisional restriction (and election) between the species of claim 89 (and its dependent claims 90-107) in the event that the generic claim is not held allowable, as discussed above.. The Examiner stated that she would confer with her SPE, Shannon Foley to determine whether it is appropriate to alter the restriction requirement to reflect an election of species requirement rather than a group requirement.

REQUEST FOR RECONSIDERATION

Pursuant to 37 C.F.R. §1.143, Applicants respectfully request reconsideration of the outstanding restriction requirement and, more specifically, Applicants respectfully request that Examiner change alter the restriction requirement to reflect an election of species rather than a group requirement. Applicant's reasoning for such request is clearly laid out in paragraphs 3-6 of the **Summary Of Interview** section (above) of this paper.

In sum, the present restriction is not proper because (1) the inventions are not

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independent or distinct *and* (2) there is not a serious burden on the Examiner if restriction is not required. See § 803 MPEP. In the instant case, Applicants have shown in the **Summary Of Interview** section that none of the claims or any elements of the claims constitute independent or distinct subject matter. Therefore, restriction (beyond provisional election of species) is not proper and Applicants are entitled to pursue claims 89-107 as originally filed.

Applicants have voluntarily agreed to *not to pursue* (without traverse) the subject matter of group A (as it pertains to claims 84-88) and group C (claims 108-110),. Applicants respectfully submit that the subject matter of group B (claims 89 and 93-107) as well as claims 90-92 constitutes a single, patentable invention that should not be subject to group restriction. Accordingly, reconsideration of the outstanding restriction as it relates to these claims is earnestly solicited. Applicants hereby provisionally elect IGPR together with NDF as species within the Markush Group recited in subparts (a)-(f) of claim 89 for prosecution on the merits in the event that the Examiner does not find the generic claim allowable. Reconsideration is particularly requested in light of the fact that other Examiners in Art Unit 1600 have (properly) not required restriction of similarly structured claims to similar subject matter in other pending cases owned by Applicants.

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Conclusion

The presently elected claims are believed to be in condition for immediate allowance. Reconsideration and alteration of the present Restriction Requirement to reflect an election of species requirement rather than an election of group requirement is respectfully requested. Early and favorable consideration and allowance of these claims is earnestly solicited. If there are any questions regarding these remarks, the Examiner is requested to call the undersigned attorney at the telephone number provided.

Respectfully submitted,



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